Practical Approach for Management of Nephrotic Syndrome

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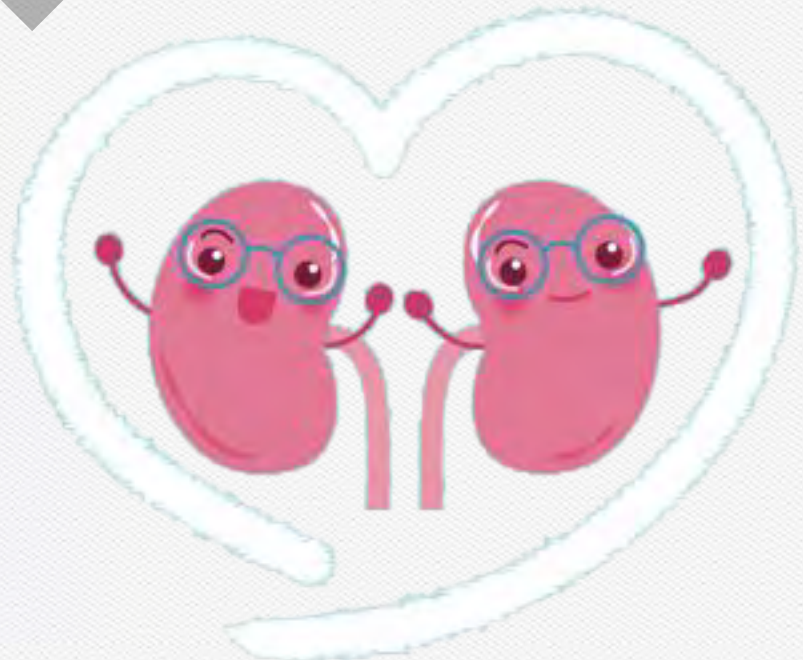
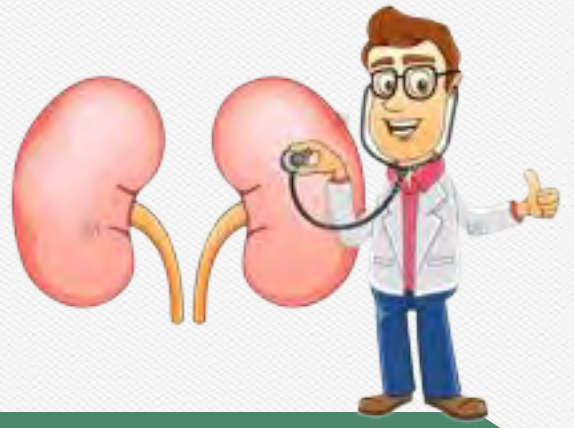


Pediatric Nephrology Center
Cairo University

Agenda

- Indications of renal biopsy in NS patients UpToDate
- Who does not deserve immunosuppressive treatment?
- Management of SSNS
- Management of SDNS
- Management of SRNS

Indications of renal biopsy



Pre-treatment

1. Age <1 or > 10 y
2. Persistent or gross hematuria
3. Severe HTN and renal dysfunction
4. Low C3
5. Extra-renal features

SRNS patients

For Cyc A therapy

After 2-3 years to detect nephrotoxicity

Who does not deserve immunosuppressive therapy

- Inherited NS is always resistant to steroids and immunosuppressive ttt, since this is not an immunologic disease.
- These drugs may be harmful due to the already high susceptibility to infection.

Non-immunosuppressive Actions Of Immunosuppressives

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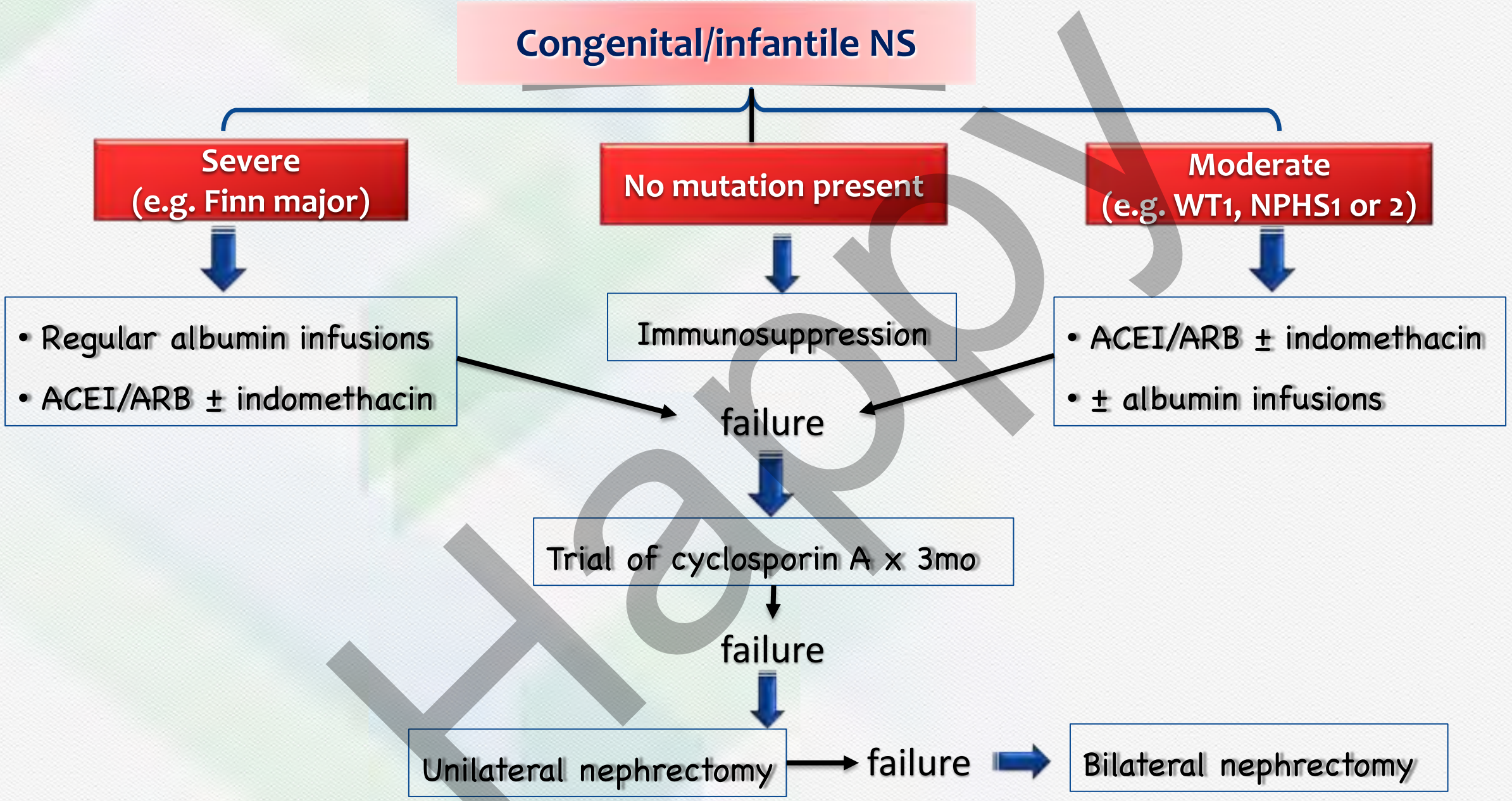
Factors affecting decision

1. Age of presentation
2. Severity of initial symptoms
3. Renal pathology
4. Genetic testing

No consensus

Kemper and Lemke. Frontiers in Pediatr 2018; 6(72): 1-8



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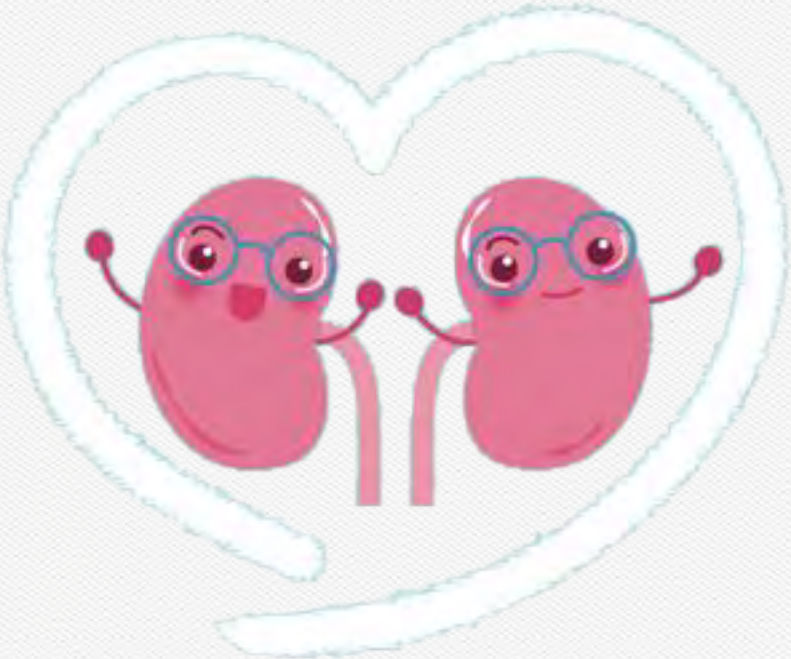
Management of SSNS



1st attack

Initiate prednisone 60 mg/m²/day divided for 4 w (max. 60mg)

SSNS

Taper gradually in alternate day basis over total 12 w duration

Remission

SDNS & Frequent relapses

Achieve remission prednisone 60 mg/m²/d till urine is free of proteins x 3Ds. Then taper gradually on alternate day basis to the patient's steroid threshold (i.e. the dose at which the relapse has occurred). This regimen is continued for 12 to 18 months.

Steroid S.E. or toxicity

Infrequent relapses

Achieve remission prednisone 60 mg/m²/d till urine is free of proteins x 3Ds. Then taper gradually over 4-8 ws.

Partial Response

3 pulses MTP **OR** continue prednisone 60 mg/m²/d for total 8 w + ACEI

If response →same dose e.o.d. for 1mo →taper over 3-6 mo.

If no complete remission

Try to achieve remission by adding CNI‡

If no complete remission

*If Relapse >30 mg/m² e.o.d.**

Add steroid sparing agent:
- MMF†
- Calcineurin inhibitors (CNI)‡
- Cyclophosphamide§
- Rituximab¶

*If Relapse <30 mg/m² e.o.d.**

Add levamisole 2.5mg/kg e.o.d.

Adequate response → continue 12 -18 m

Failed to maintain remission

3 pulses MTP

SRNS

Renal biopsy + Plan A

ACEI= angiotensin converting enzyme inhibitors
MMF=mycophenolate mofetil
SDNS=steroid dependent nephrotic syndrome
SRNS= steroid resistant nephrotic syndrome
SSNS= steroid sensitive nephrotic syndrome

*Use the smallest dose of prednisone keeping patient in remission and avoiding toxicity
† **MMF**:1200 mg/m²/d
‡ **CNI:**
- Cyclosporine 5 mg/kg/d (trough level 100-150 ng/ml)
- Tacrolimus 0.15 mg/kg/d (trough level 5-10 ng/ml)

§**Cyclophosphamide** 2mg/kg/d for 12 w (cumulative dose 168 mg/kg)
¶**Rituximab**:375 mg/m²/w x 4 doses

1st attack

Initiate prednisone 2mg/kg/day divided for 4 w (max. 60mg)

SSNS

Taper gradually in alternate day basis over total 12 w duration

- **Complete remission**
- **SDNS & frequent relapses**

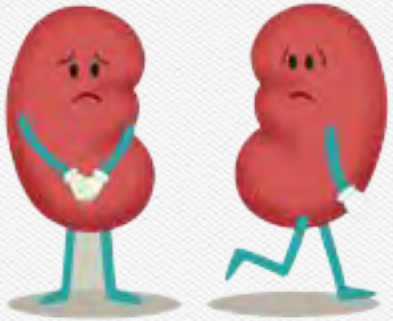
Partial Response

(<50% reduction in Ur. Protein)

3 pulses MTP

SRNS

Length of therapy & risk of relapse



Treatment durations of 2-3 mo are recommended for the management of the first episode of SSNS rather than longer durations, as recommended in the KDIGO guidelines

Steroid-sensitive nephrotic syndrome: an evidence-based update of immunosuppressive treatment in children. Arch Dis Child 2016; 101:404.

SSNS

Complete remission

Infrequent relapses

Achieve remission prednisone 2mg/kg/d till urine is free of proteins x 3Ds. Then taper gradually over 4-8 ws.

SDNS & frequent relapses

Achieve remission prednisone 2mg/kg/d till urine is free of proteins x 3Ds. Then taper gradually on alternate day basis to the patient's steroid threshold. This regimen is continued for 12 to 18 months.

Steroids S.E. or toxicity

SDNS & Frequent Relapses

Steroids S.E. or toxicity

Relapse >1mg/kg e.o.d

Add Steroid sparing agent

- MMF
- Cyclophosphamide
- Cyclosporin A
- Rituximab

Relapse <1mg/kg e.o.d

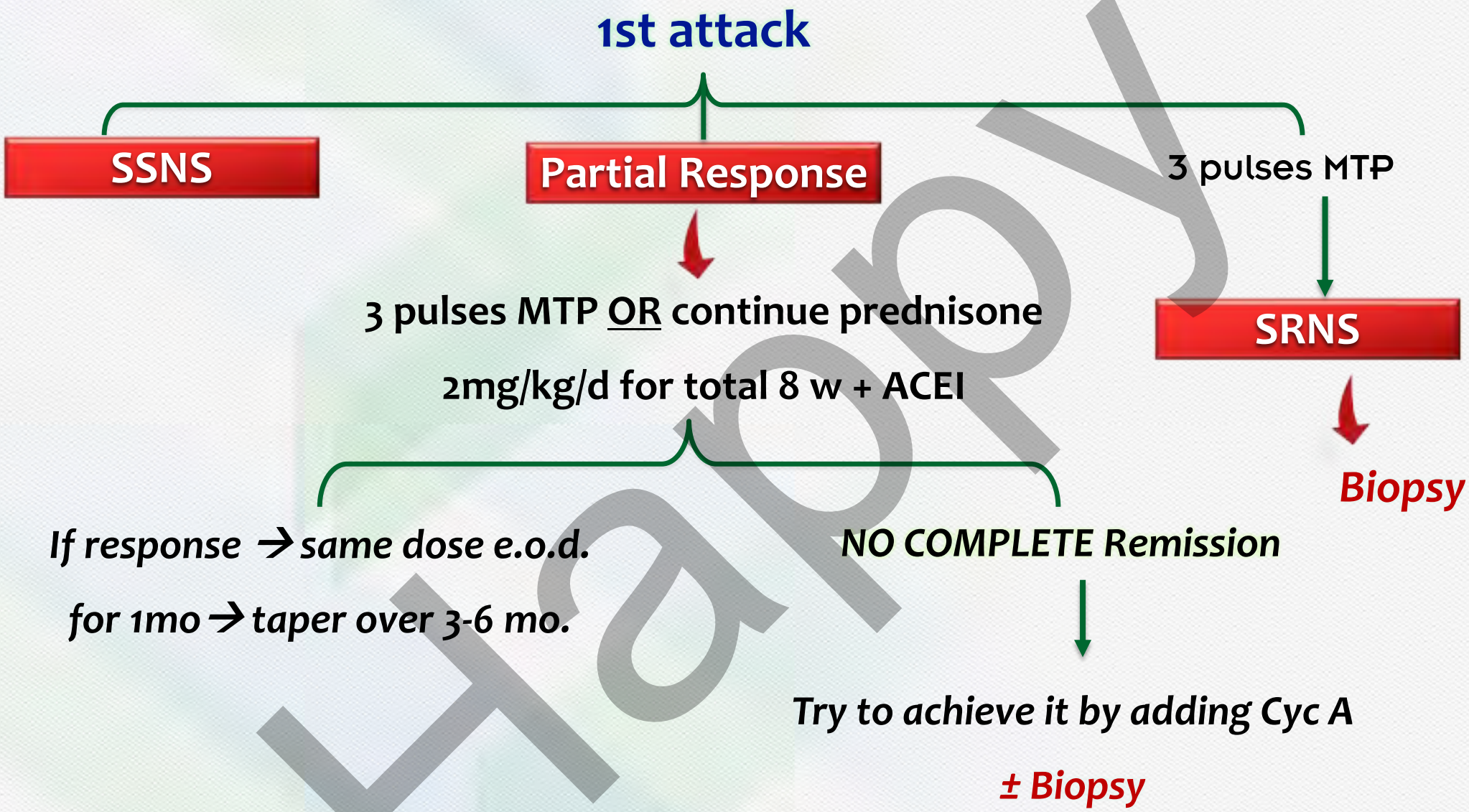
Add levamisole 2.5 mg/kg e.o.d.

Failed to maintain remission

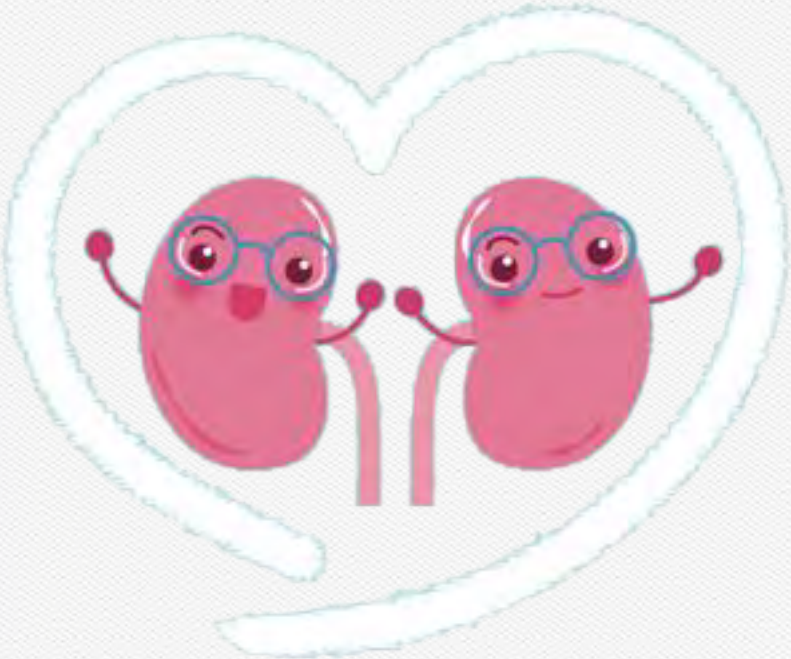
Adequate Response

Continue 12-18 mo

Viral URTI may trigger a relapse so a short-term increase to daily steroid rather than alternate day therapy is needed

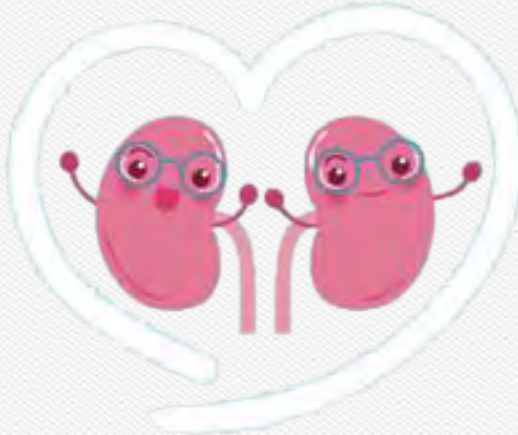

1st attack
SSNS
Partial Response
3 pulses MTP
3 pulses MTP OR continue prednisone
2mg/kg/d for total 8 w + ACEI
SRNS
Biopsy
If response → same dose e.o.d.
for 1mo → taper over 3-6 mo.
NO COMPLETE Remission
Try to achieve it by adding Cyc A
± Biopsy

Management of SRNS



Cochrane Library

Cochrane Database of Systematic Reviews



Interventions for idiopathic steroid-resistant nephrotic syndrome in children (Review)

Hodson EM, Wong SC, Willis NS, Craig JC

Alkylating agents — There are **no** data showing a beneficial effect of alkylating agents in children with SRNS. Partial or complete remissions have been reported in 20 percent of cases following a course of cyclophosphamide, but this is similar to the remission rate of nontreated patients or that of those who continue to receive steroid therapy alone [2,5,27,31,32].

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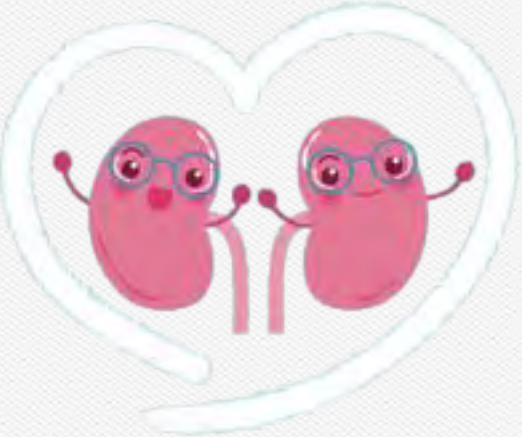

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Plan A

Cyclosporine P.O. 150 mg/m²/day in 2 divided doses for 24 w

+

Prednisone 30 mg/m²/day for 4 w then 30 mg/m² e.o.d

If remission is achieved

↓

cyclosporine is tapered to a minimal effective dose

If NO Response

Add ACEI/ARB (if not added previously)

↓

If NO Response

↓

Add MMF 1200 mg/m²/d for 12 ws

If no response

??

- Stop immunosuppressives
- ACEI/ARB
- RCTs

If response

cyclosporine is tapered to a minimal effective dose

& continue MMF 12 mo

SRNS

In MCGN, MgPGN, IgM nephropathy OR

When the biopsy is not feasible

Cyclosporine P.O. 5mg/kg/day in 2 divided doses for 24 w

+

Prednisone 1 mg/kg/day for 4 w then 1 mg/kg e.o.d

If remission is achieved

cyclosporine is tapered to a minimal effective dose

If no response

??

- Stop immunosuppressives
- RCTs

If response

cyclosporine is tapered to a minimal effective dose

& continue MMF 12 mo

If NO response

Add ACEI/ARB if not added before

If NO response

Add MMF 1200 mg/m²/d for 12 ws

SRNS

FSGS

↓

The same protocol

+

Antifibrotic agents (spironolactone)

+

Anti-oxidants (Vit.E)

↓

If Failed

↓

??Plasmapheresis 6 sessions over 2w

↓

If Failed →

- **Stop immunosuppressives**
- **RCTs**

CONCLUSION

- Immunosuppressives (e.g. cyclosporin) may have a role in inherited NS.
- Short-course of steroids as effective as long-course in management of SSNS.
- Watch for steroids and cyclosporin toxicity during treatment.
- After exhaustion of immunosuppressives in SRNS, no need to continue on immunosuppressives.

❖ **Which of the following NOT indicated for renal biopsy:**

a. A 12-year-child with NS

b. NS in an infant with ambiguous genitalia

c. A child with 5 relapses/year

d. Hematuria in child previously known to have SSNS

❖ **The whole duration of steroid therapy in patients with infrequent relapses is:**

a. 4-8 weeks
b. 2-3 months
c. 3-6 months
d. 12 months

❖ **The duration needed to assess cyclosporin efficacy is:**

a. 2 months

b. 3 months

c. 6 months

d. 12 months